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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.:	PENN-0789
Inventors:	Siegel et al.
Serial No.:	10/046,504
Filing Date:	October 19, 2001
Examiner:	Fubara, Blessing M.
Customer No.:	26259
Group Art Unit:	1615
Confirmation No.:	3358
Title:	Polymer-based Surgically Implantable Haloperidol Delivery Systems and Methods for Their Production and Use

Declaration by Steven Siegel

I, Steven Siegel, hereby declare:

1. I am a co-inventor of the above-referenced patent application for implantable haloperidol delivery systems.

2. I have reviewed the Office Action mailed October 19, 2006 in the above-referenced patent application and in particular the Examiner's remarks regarding the antipsychotic agent clozapine being incorporated into our implant.

3. We tried to create clozapine implants using the methods and knowledge related to haloperidol implants disclosed in the above-referenced patent application.

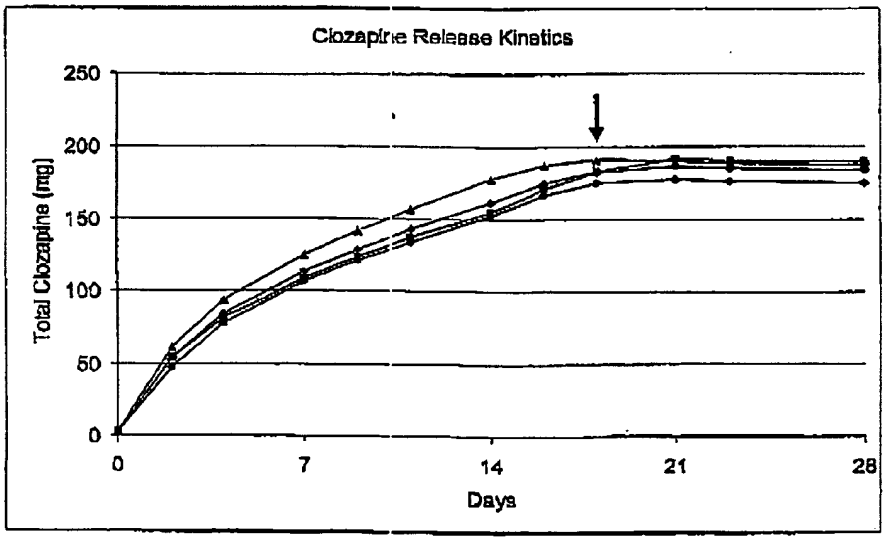
4. We initially designed clozapine implants with a goal to release the active drug (clozapine) for 30 days using 50:50 PLGA with 20% drug load. This approach achieved 30 day release of haloperidol using the same polymer composition, design, fabrication methods and drug loads.

5. A problem arose during fabrication, however, because clozapine is not soluble in the same solvents as PLGA. Therefore, composite solvents containing both ethanol and

acetone were required to form a solution containing both materials. The resulting composite material is likely composed of a less homogeneous mixture of drug and polymer due to differing solubility as the composition of the mixed solvent changes during the evaporation process (i.e. ethanol and acetone components will evaporate at different rates, likely causing unequal precipitation of the drug (clozapine) and polymer (PLGA).

6. A second difficulty arose during molding. Clozapine implants were soft and gooey at processing temperatures and conditions needed to mold PLGA. In contrast, haloperidol implants were hard and did not stick to molds or deform during this process. Thus it was far more difficult to form fully dense implants that did not deform or adhere to the Teflon coated molds with clozapine.

7. Despite these difficulties, we tested the clozapine implants in vitro to examine the effects of the aforementioned differences in processing properties due to the physical characteristics of the drug. As demonstrated below, clozapine implants were only capable of releasing drug for 18 days (arrow), which was approximately 60% of the interval achieved for haloperidol using the same approach. Thus, clozapine was not sufficiently similar to haloperidol to allow generalization of the methods for creating implants. Each line in the figure represents a replicate pellet (n=3) or their average.



8. Furthermore, we examined the ability of the clozapine implants to release drug in rats for 18 days. As shown in the

following table, these experiments revealed highly variable release with inconsistent serum levels of clozapine with implants prepared via a similar method to the haloperidol implants. These results differed significantly from our experience with haloperidol implants, which yield highly consistent release and serum levels in vivo. Note that the variability for clozapine implants as measured by the standard deviation between animals was equal to the mean value, indicating an unacceptable level of variability for clozapine implants prepared via a similar method to the haloperidol implants.

Implant	Serum level in rat (ng/ml)
clozapine implant 1	0.016
clozapine implant 2	0.177
clozapine implant 3	0.199
clozapine implant 4	0.204
clozapine implant 5	0.181
clozapine implant 6	0.442
clozapine implant 7	0.449
clozapine implant 8	0.437
clozapine implant 9	2.013
clozapine implant 10	0.637
clozapine implant 11	0.514
clozapine implant 12	0.753
clozapine implant 13	0.842
clozapine implant 14	0.523
clozapine implant 15	0.252
clozapine implant 16	0.245
clozapine implant 17	1.276
Mean	0.49
Standard deviation	0.49

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Steven J. Siegel

12/12/06
Date